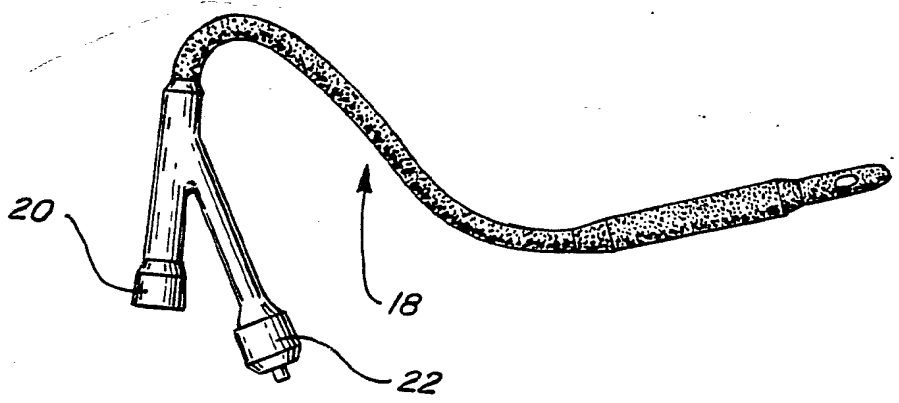




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US83/01404 (22) International Filing Date: 15 September 1983 (15.09.83) (31) Priority Application Number: 439,506 (32) Priority Date: 5 November 1982 (05.11.82) (33) Priority Country: US (71) Applicant: BAXTER TRAVENOL LABORATORIES, INC. [US/US]; One Baxter Parkway, Deerfield, IL 60015 (US). (72) Inventors: LAURIN, Dean, G. ; 564 Applegate Lane, Lake Zurich, IL 60047 (US). STUPAR, James ; 395 Poplar Street, Crystal Lake, IL 60014 (US). (74) Agents: CARUSO, John, A. et al.; One Baxter Parkway, Deerfield, IL 60015 (US).		(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i>
(54) Title: ANTIMICROBIAL COMPOSITIONS		
		
(57) Abstract Antimicrobial compositions finding particular utility for coating access systems, lead devices including shunts, canulae, catheters (18), catheter adapters, wires and other solid or hollow tubular devices used for a variety of medical purposes. The composition comprises a material selected from the group consisting of acrylonitrilebutadiene-styrene copolymers, polyvinyl chloride, mixtures thereof, polyesters, polyurethanes, styreneblock copolymers, natural and synthetic rubbers, polycarbonates, nylon and silicone rubber mixed with an oligodynamic material consisting essentially of physiological, antimicrobial metals.		

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ANTIMICROBIAL COMPOSITIONSField of the Invention

This invention relates to compositions useful in making medical devices and useful in providing antimicrobial coatings on medical devices. The invention particularly relates to antimicrobial compositions useful as coatings for medical connection devices and for making medical connection devices which are susceptible to touch contamination. These compositions are also useful as antimicrobial coatings for access systems and lead devices (for example, shunts, cannulae, catheters, wires, enteral feeding tubes, endotracheal tubes, percutaneous devices and other solid or hollow tubular devices) used for a variety of medical purposes. In addition, the compositions may be used as antimicrobial coatings for wound coverings or in the manufacture of thin, flexible, skin-like wound coverings.

Background of the Invention

Indwelling urethral catheterization is performed in approximately 10 to 15 percent of hospitalized patients. About 25 percent of these patients contract bacterial infections of the urinary tract. Two studies of note are, Garibaldi, R. A.; Burke, J. P.; Dickman, M. L.; and Smith, C. B., "Factors Predisposing to Bacteriuria During Indwelling Urethral Catheterization". New Engl. J. Med., 291:215, 1974 and Kunin, C. M. and McCormack, R. C., "Prevention of Catheter-Induced Urinary-Tract Infections by Sterile Closed Drainage". New Engl. J. Med., 274:1155, 1966.

The incidence of catheter-induced urinary tract infection still remains a problem despite various prophylactic measures that have been tried. Attempts to



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reduce the incidence of urinary tract infections have included the application of antibiotic ointments or other bactericidal agents to the surface of the catheter, frequent bladder irrigation with concomittant prophylactic administration of antibiotics, or inhibition of the growth of bacteria in urine drainage containers. See, Akiyama, H. and Okamoto, S., "Prophylaxis of Indwelling Urethral Catheter Infection: Clinical Experience with a Modified Foley Catheter and Drainage System". The Journal of Urology, 121:40, 1979. United States Patent No. 4,054,139, Oligodynamic Catheter, to Crossley, teaches a catheter, or the like, which comprises an oligodynamic agent such as metallic silver or its compounds, alone or in association with other heavy metals such as gold, for the purpose of reducing infection associated with these devices.

It would be desirable to provide compositions useful as coatings for urinary catheters, lead devices, medical connections susceptible to touch contamination and the like, and compositions useful as a material for making these various devices, whereby the proliferation of bacteria thereon or in relatively close proximity thereto is inhibited. Inhibiting the proliferation of bacteria on urinary catheters and catheter adapter connections would reduce the risk of urinary tract infections caused by bacteria accessing the urinary tract at these sites. It also would be desirable for the compositions to be easily applied as coatings on presently existing medical connections and devices. A desirable characteristic of such a composition would be an antimicrobial effect which is long lasting without being physiologically incompatible with nearby tissue.



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Description of the Invention

In accordance with this invention, antimicrobial compositions are provided which find particular utility as coatings which inhibit the proliferation of bacteria near the surface of urinary catheters and the connection between the catheter and the drainage tube, namely, the catheter/catheter adapter junction site. The antimicrobial coating on the catheter inhibits the proliferation of bacteria in the area between the catheter and the walls of the urethra, and the antibacterial coating on the catheter adapter inhibits the proliferation of bacteria in the closed area connecting the catheter and the catheter adapter.

Catheters implanted in patients undergoing continuous ambulatory peritoneal dialysis also can be coated with an antimicrobial composition of this invention. An antimicrobial composition of this invention can be applied as a coating to medical shunts, cannulae, catheters, wires and other solid or hollow tubular devices used for medical purposes.

Preferably, the coating using an antimicrobial composition is prepared by mixing a suitable resin and a compound of a physiological, antimicrobial metal in an appropriate solvent for the resin. The solvent should not adversely effect the activity of the metal compound as an antimicrobial agent. The coating can be applied to a medical device by dipping in the mixture of resin, solvent, and physiological, antimicrobial metal compound and thereafter allowing the solvent to evaporate. Both inside and outside surfaces may be coated. Alternatively, the medical articles may be sprayed with the mixture and the solvent allowed to evaporate. Where appropriate, particularly with a latex rubber resin, a volatile liquid carrier may be



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used with the resin dispersed in the volatile liquid. An article may be dipped or sprayed with this preparation. Upon evaporation of the volatile liquid and curing of the resin a coating for the article is provided.

Indeed, articles can be made from a composition of a suitable resin and a compound of physiological, antimicrobial metal by molding the composition to form the article.

The resins used in formulating the mixture include, for example, acrylonitrile-butadiene-styrene copolymer, rigid polyvinyl chloride, curable silicones, alkoxy cured RTV silicone rubber, polyesters, rubber latexes (e.g., natural or synthetic polyisoprene), polyurethanes, styrene-block copolymers (e.g., Kraton-D and Kraton-G, manufactured by Shell), ethylene copolymers (e.g., vinyl acetate, ethyl acrylate, or mixtures thereof), ethylene copolymers of maleic anhydride, acrylic acid or both, polycarbonates, nylons, and polymethyl methacrylate.

Into a mixture of resin and solvent is added a quantity of physiological, antimicrobial metal compound. Alternatively, a quantity of physiological, antimicrobial metal compound may be mixed with a resin for direct molding of an article. Physiological, antimicrobial metals are meant to include the precious metals, such as silver, gold and platinum, and copper and zinc. Physiological, antimicrobial metal compounds used herein include oxides and salts of preferably silver and also gold, for example: silver acetate, silver benzoate, silver carbonate, silver citrate, silver chloride, silver iodide, silver oxide, silver sulfate, gold chloride and gold oxide. Platinum compounds such as chloroplatinic acid or its salts (e.g., sodium and calcium chloroplatinate) may also be used. Also, compounds of



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copper and zinc may be used, for example: oxides and salts of copper and zinc such as those indicated above for silver. Single physiological, antimicrobial metal compounds or combinations of physiological, antimicrobial metal compounds may be used.

Preferred physiological, antimicrobial metal compounds used in this invention are silver acetate, silver oxide, silver sulfate, gold chloride and a combination of silver oxide and gold chloride. Preferred quantities of physiological, antimicrobial metal compound are those sufficient to produce, within a 24 hour period, a solution of at least 10^{-6} molar concentration of metal ion concentration in a stagnant film of liquid in contact with a surface of an article made from a composition of this invention or an article coated with a composition of this invention.



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Brief Description of the Drawings

For a more complete understanding of this invention, reference should now be had to the embodiments illustrated in greater detail in the accompanying
5 drawings.

In the drawings:

Figure 1 is an elevational view of a catheter adapter showing one end coated with an antimicrobial composition of this invention.

10 Figure 2 is an elevational view of a Foley catheter showing the portion of the catheter typically inserted into the urethra, coated with an antimicrobial composition of this invention.

15 Figure 3 is a perspective view of the catheter adapter of this invention shown connecting a urinary drainage tube and a catheter.



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Detailed Description of the Drawings

Turning now to the drawings, Figure 1 shows a conventional catheter adapter 10 after it has been coated with an antimicrobial composition of this invention. Catheter adapter 10 has drainage tube end 12, catheter end 14, and injection site 16.

Catheter end 14 is spray coated or dip coated with an antimicrobial composition of this invention. The shaded portion of catheter end 14 is illustrative of the coating.

Figure 2 shows urinary catheter 18. Catheter 18 has drainage connection 20 and inflation connection 22 for inflating the catheter balloon.

The shaded portion of catheter 18 illustrates the area coated by an antimicrobial composition of this invention. Typically, this coating will be applied to that portion of catheter 18 which resides in the urethra of a patient.

A typical connection of catheter adapter 10 is illustrated in Figure 3. Catheter adapter 10 has the coated catheter end 14 connected to drainage connection 20 of the catheter. Drainage tube end 12 is connected to drainage tube 24 to complete the connection. Drainage tube 24 drains into a urinary drainage bag (not shown).

The risk of touch contamination of catheter end 14 is reduced by coating catheter end 14 of catheter adapter 10 with an antimicrobial composition of the present invention. Reducing the risk of touch contamination of catheter end 14 reduces the risk of subsequent urinary tract infection caused by a contaminated catheter adapter.

The antimicrobial composition coating catheter 18 inhibits the proliferation and migration of bacteria



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in a stagnant film between the coated catheter walls and the walls of the urethra. By inhibiting the proliferation and migration of bacteria through this route, subsequent urinary tract infection caused by such proliferation and migration of bacteria is reduced.

The examples below are offered for illustrative purposes only and are not intended to limit the scope of the invention of this application, which is as defined in the claims below.

EXAMPLE 1

A mixture was made of 50 milliliters of methylene chloride, 5 grams of acrylonitrile-butadiene-styrene copolymer (LUSTRAN 240-29, a trademark of the Monsanto Company), and 1.2 grams of silver oxide powder. The mixture was stirred for approximately one hour. A polyvinyl chloride catheter adapter, used to connect a urinary catheter and drainage tubing for a urinary drainage connector, was coated on the exterior and the interior by dipping the connector into the mixture. Upon evaporation of the solvent, an antimicrobial coating remained bonded to the catheter adapter. Catheter adapters can also be sprayed with the mixture.

EXAMPLE 2

A mixture was made by combining 50 milliliters of tetrahydrofuran, 5 grams of polyvinyl chloride (Alpha Plastics and Chemicals, clear rigid vinyl 2212/7-118), and 1.2 grams of silver oxide powder. The mixture was stirred for about one hour.

Vinyl compatible catheter adapters may be either dip coated or spray coated with this mixture. By dip coating the catheter adapter, the exterior and interior



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surfaces may be conveniently coated. Upon evaporation of the solvent, tetrahydrofuran, an antimicrobial coating will remain bonded to the device.

EXAMPLE 3

5 Equivalent results may be obtained when a mixture is made by combining 25 milliliters of tetrahydrofuran, 25 milliliters of methylene chloride, 2.5 grams of acrylonitrile-butadiene-styrene copolymer (LUSTRAN 240-29), 2.5 grams of polyvinyl chloride (Alpha Plastics
10 and Chemicals, clear rigid vinyl 2212/7-118), and 1.2 grams of silver oxide powder. The mixture may be stirred for about one hour.

A catheter adapter may be either dip coated or spray coated with this mixture. Upon evaporation of
15 the solvents, an antimicrobial coating will remain bonded to the device.

EXAMPLE 4

A mixture was made by combining 10 milliliters of alkoxy curing RTV rubber, 65 milliliters of FREON TF
20 solvent (FREON is a trademark of E. I. du pont de Nemours & Co.), and 5 grams of silver oxide powder. The mixture was stirred for about one hour.

A silicone rubber Foley catheter was dipped into this mixture and upon evaporation of the solvent and
25 curing of the RTV, a flexible, antimicrobial coating on the interior and exterior surfaces of the silicone rubber catheter was provided. The coating adhered well to the catheter. Spray coating of the catheter is a viable alternative.

30

EXAMPLE 5

A mixture was made by combining 100 milliliters



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of tetrahydrofuran, 5 grams of acrylonitrile-butadiene-styrene copolymer (LUSTRAN 240-29), and 1 gram of silver acetate. The mixture was stirred for about one hour. Acrylonitrile-butadiene-styrene compatible devices may
5 be spray or dip coated with the mixture. Upon evaporation of the solvent, an antimicrobial coating will remain on the device.

EXAMPLE 6

Equivalent results may be obtained when a mixture
10 is made by combining 100 milliliters of methylene chloride, 5 grams of acrylonitrile-butadiene-styrene copolymer (LUSTRAN 240-29), and 1 gram of silver sulfate. The mixture may be stirred for about one hour. Acrylonitrile-butadiene-styrene compatible devices may be spray or dip
15 coated with the mixture. Upon evaporation of the solvent, an antimicrobial coating will remain on the device.

EXAMPLE 7

Equivalent results may be obtained when a mixture is made by combining 50 milliliters of tetrahydrofuran,
20 5 grams of polyvinyl chloride (Alpha Plastics and Chemicals, clear rigid vinyl 2212/7-118), and 1.2 grams of gold chloride powder. The mixture may be stirred for about one hour. Polyvinyl chloride compatible devices may be spray or dip coated with the mixture. Upon
25 evaporation of the solvent, an antimicrobial coating will remain on the device.

EXAMPLE 8

Equivalent results may be obtained when a mixture is made by combining 25 milliliters of tetrahydrofuran,
30 25 milliliters of methylene chloride, 2.5 grams of acrylonitrile-butadiene-styrene copolymer (LUSTRAN



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240-29), 2.5 grams of polyvinyl chloride (Alpha Plastics and Chemicals, clear rigid vinyl 2212/7-118), and 1.2 grams of gold chloride powder. The mixture may be stirred for about one hour. Devices may be either dip coated
5 or spray coated with this mixture. Upon evaporation of the solvents, an antimicrobial coating remains bonded to the device.

EXAMPLE 9

Equivalent results may be obtained when a mixture
10 is made by combining 10 milliliters of alkoxy curing RTV, 65 milliliters of FREON TF solvent and 5 grams of gold chloride powder. The mixture may be stirred for about one hour.

A silicone rubber Foley catheter or other silicone
15 rubber medical device may be dipped into this mixture and upon evaporation of the solvent and curing of the RTV, a flexible, antimicrobial coating for the silicone rubber catheter will be provided. Spray coating of the catheter is also a viable alternative.

EXAMPLE 10

20 Equivalent results may be obtained when a mixture is made by combining 50 milliliters of tetrahydrofuran, 5 grams of polyvinyl chloride (Alpha Plastics and Chemicals, clear rigid vinyl 2212/7-118), 1.2 grams
25 of silver oxide powder, and 0.1 gram of gold chloride powder. The mixture may be stirred for about one hour.

Vinyl compatible catheter adapters or other medical devices may be either dip coated or spray coated with this mixture. Upon evaporation of the solvent,
30 tetrahydrofuran, an antimicrobial coating will remain on the device.



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EXAMPLE 11

Equivalent results may be obtained when a mixture is made by combining 25 milliliters of tetrahydrofuran, 25 milliliters of methylene chloride, 2.5 grams of acrylonitrile-butadiene-styrene copolymer (LUSTRAN 240-29), 2.5 grams of polyvinyl chloride (Alpha Plastics and Chemicals, clear rigid vinyl 2212/7-118), 1.2 grams of silver oxide powder, and 0.1 gram of gold chloride powder. The mixture may be stirred for about one hour.

10 Devices may be either dip coated or spray coated with this mixture. Upon evaporation of the solvents, an antimicrobial coating will remain on the device.

EXAMPLE 12

Equivalent results may be obtained when a mixture is made by combining 10 milliliters of alkoxy curing RTV, 65 milliliters of FREON TF solvent, 5 grams of silver oxide powder, and 0.5 gram of gold chloride powder. The mixture may be stirred for about one hour.

20 A silicone rubber Foley catheter or other silicone rubber medical device may be dipped into this mixture and upon evaporation of the solvent and curing of the RTV, a flexible, antimicrobial coating for the silicone rubber catheter is provided. Spray coating of the

25 catheter is also an alternative application means.

EXAMPLE 13

Equivalent results may be obtained when a mixture is made by combining 100 milliliters of natural rubber latex with 10 grams of silver oxide powder. The mixture may be stirred until the silver oxide is dispersed.

30 Cured latex rubber devices may be dip coated with this



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mixture. Upon evaporation of the volatile liquid carrier and curing of the coating mixture, an antimicrobial coating having high elastomeric characteristics will remain adhered to the device.

5

EXAMPLE 14

Equivalent results may be obtained when a mixture is made by combining 50 milliliters of methylene chloride, 5 grams of acrylonitrile-butadiene-styrene copolymer (LUSTRAN 240-29), and 1.2 grams of copper oxide powder. The mixture may be stirred for about one hour. A catheter adapter may be either dip coated or spray coated with this mixture. Upon evaporation of the solvent, an antimicrobial coating will remain bonded to the device.

15

EXAMPLE 15

Equivalent results may be obtained when a mixture is made by combining 50 milliliters of methylene chloride, 5 grams of acrylonitrile-butadiene-styrene copolymer (LUSTRAN 240-29), and 1.2 grams of zinc oxide powder. The mixture may be stirred for about one hour. A catheter adapter may be either dip coated or spray coated with this mixture. Upon evaporation of the solvent, an antimicrobial coating will remain bonded to the device.

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1. An antimicrobial composition comprising:

30 to 85 percent by weight of a binder consisting essentially of a material selected from the group consisting of acrylonitrile-butadiene-styrene copolymers, polyvinyl chloride, mixtures thereof, polyesters, polyurethanes, styrene-block copolymers, natural and synthetic rubbers, polycarbonates, nylon and silicone rubber; and,

15 to 70 percent by weight of an antimicrobial agent selected from the group consisting of compounds of physiological, antimicrobial metals and mixtures thereof.

2. The antimicrobial composition of Claim 1 in which said mixtures of acrylonitrile-butadiene-styrene copolymers and polyvinyl chloride consist of 25 to 75 percent by weight of acrylonitrile-butadiene-styrene copolymers and 25 to 75 percent by weight of polyvinyl chloride.

3. The antimicrobial composition of Claim 1 in which said antimicrobial agent is selected from the group consisting of oxides and salts of silver and gold.

4. The antimicrobial composition of Claim 1 in which said antimicrobial agent is selected from the group consisting of silver compounds.

5. The antimicrobial composition of Claim 4 in which said antimicrobial agent is silver oxide.

6. An antimicrobial composition for coating articles comprising:

30 to 85 percent by weight of a binder consisting essentially of acrylonitrile-butadiene-styrene copolymers; and,

15 to 70 percent by weight of an antimicrobial agent selected from the group consisting essentially of silver compounds and mixtures thereof whereby the particles of silver compound are exposed on the coating



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layer on the surface of the article and being sufficiently mobile to produce, within 24 hours, a solution of at least 10^{-6} molar concentration of silver ion concentration in a stagnant film of urine in contact with said surface.

- 5 7. An antimicrobial composition for coating articles comprising:

30 to 85 percent by weight of a binder consisting essentially of a mixture consisting of 35 to 65 percent by weight of acrylonitrile-butadiene-styrene copolymers
10 and 35 to 65 percent by weight of polyvinyl chloride; and,

15 to 70 percent by weight of an antimicrobial agent consisting essentially of silver oxide whereby the particles of silver oxide are exposed on the coating
15 layer on the outermost surface of the article and being sufficiently mobile to produce, within 24 hours, a solution of at least 10^{-6} molar concentration of silver ion concentration in a stagnant film of urine in contact with said surface.

- 20 8. The antimicrobial composition of Claim 7 in which said mixtures of acrylonitrile-butadiene-styrene copolymers and polyvinyl chloride consist of 50 percent by weight of acrylonitrile-butadiene-styrene copolymers and 50 percent by weight of polyvinyl chloride.



FIG. 1

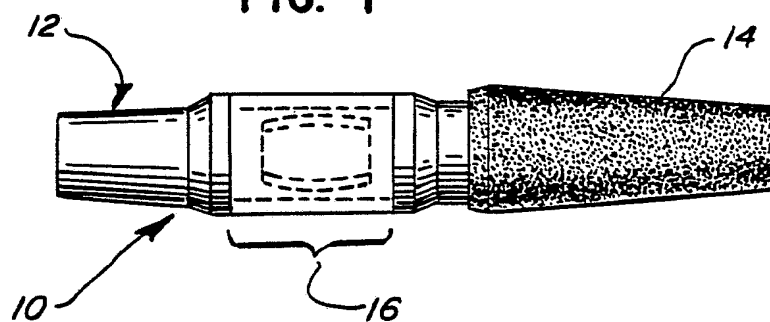


FIG. 2

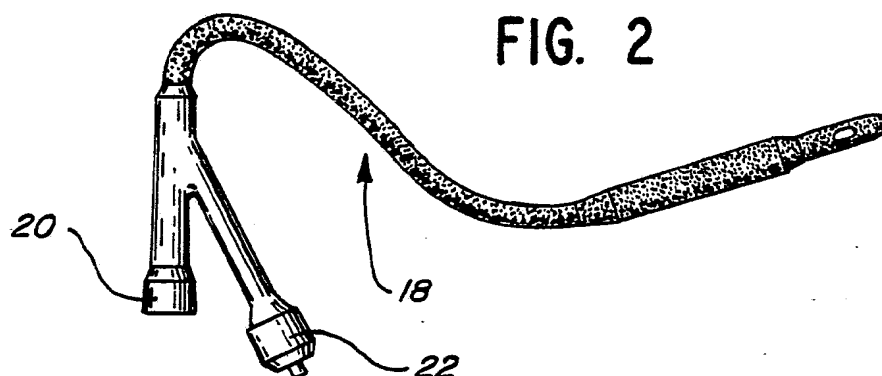
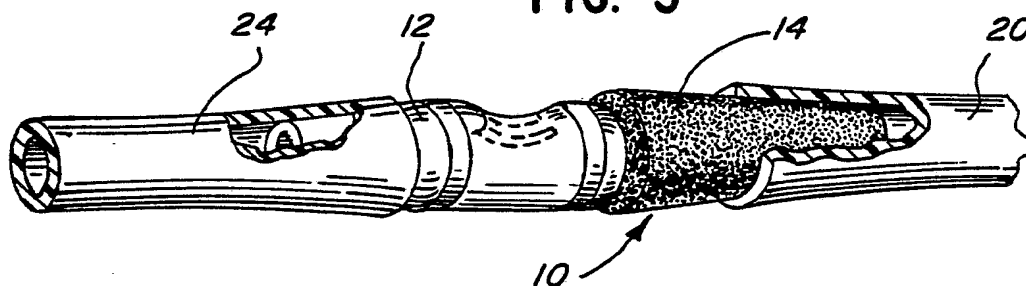
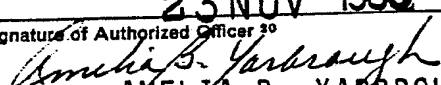


FIG. 3



INTERNATIONAL SEARCH REPORT

International Application No PCT/US83/01404

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ³ A61M 25/00		
U.S. 523/122		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	523/122 106/15.05, 16	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category *	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X	US, A, 2,785,106, PUBLISHED 12 MARCH 1957, MENDELSON	1-8
X	US, A, 2,813,059, PUBLISHED 12 NOVEMBER 1957, DAVIS ET AL	1-8
X	US, A, 3,396,727, PUBLISHED 13 AUGUST 1968, MOUNT	1-8
X	US, A, 3,566,874, PUBLISHED 2 MARCH 1971, SHEPHERD ET AL	1-8
X	US, A, 2,521,713, PUBLISHED 12 SEPTEMBER 1950, GOETZ	1-8
X	US, A, 4,027,393, PUBLISHED 7 JUNE 1977, ELLIS ET AL	1-8
X	US, A, 3,695,921, PUBLISHED 3 OCTOBER 1972, SHEPHERD ET AL	1-8
X	US, A, 4,054,139, PUBLISHED 18 OCTOBER 1977, CROSSLEY	1-8
<p>* Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ²	Date of Mailing of this International Search Report ²	
4 NOVEMBER 1983	23 NOV 1983	
International Searching Authority ¹	Signature of Authorized Officer ²⁰	
ISA/US	 AMELIA B. YARBROUGH	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X

N, THE NEW ENGLAND JOURNAL OF MEDICINE,
ISSUED 26 MAY, 1966, CALVIN M. KUNIN ET AL,
PREVENTION OF CATHETER-INDUCED URINARY-TRACT
INFECTIONS BY STERILE CLOSED DRAINAGE,
SEE PAGE 1155

1-8

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹⁰

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers....., because they relate to subject matter¹² not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out¹³, specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ¹¹

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.